ment translates into greater net angiographic gain at six months. In accordance with these observations, the principal determinant of an improved coronary lumen at six months was the minimal diameter of the lumen after the procedure, whichever device is used to achieve it. The fact that patients undergoing atherectomy had a significantly higher rate of early success and a large post-procedural lumen that could not be obtained as frequently with balloon angioplasty probably explains the angiographic benefit of atherectomy in this trial. These results support the thesis that removing the coronary atherosclerotic lesion by directional atherectomy can produce a more widely patent arterial lumen, particularly in the left anterior descending coronary artery, thereby inviting further investigation of mechanical approaches to reducing restenosis. Of course, methods of modifying the underlying biologic response to vessel-wall injury, including the change of phenotype in smooth-muscle cells and the aggressive inflammatory response seen after these procedures, will also be required.[28]

Atherectomy resulted in a higher rate of early complications, chiefly consisting of abrupt vessel closure and non–Q-wave myocardial infarction. Because of the excess of periprocedural infarction and death during follow-up, the results for the clinical end point of death and nonfatal myocardial infarction were worse with atherectomy. The trial tested a rather broad application of coronary atherectomy; patients were enrolled on the basis of their suitability for either procedure, and the angiographic data indicate that atherectomy was not performed aggressively. In particular, it is impossible to know whether more plaque retrieval, probably reducing restenosis further, would have worsened or improved the rate of procedural complications. In other studies of atherectomy, larger post-procedural lumen diameters and lower rates of restenosis were obtained without substantially higher complication rates.[19,26] The optimal "therapeutic window" of atherectomy may thus require further definition in prospective, randomized trials.

Although atherectomy led to greater initial gain in lumen size and a small reduction in the rate of restenosis, this angiographic benefit was overshadowed by the increase in adverse clinical outcomes and cost. Removing plaque rather than dilating the diseased coronary artery thus remains an attractive concept, but balloon angioplasty is still the preferred approach overall unless and until techniques of atherectomy can be improved or until convincing, reproducible findings indicate that certain subgroups will benefit from atherectomy from a clinical as well as an angiographic standpoint.

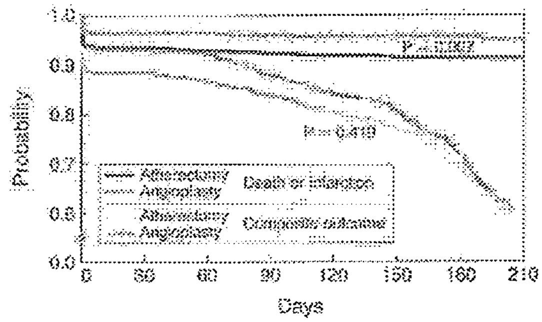

Figure 2. Kaplan–Meier Survival Curves for Patients Undergoing Atherectomy or Angioplasty, with Regard to Major Clinical Outcomes.

Survival curves are shown for the probability of death and myocardial infarction (P = 0.007) and for a composite outcome including death, myocardial infarction, coronary artery bypass surgery, and the need for subsequent coronary intervention (P = 0.419).

Table 4. Cumulative Clinical Outcomes at the Six-Month Follow-up.*

Outcome	Atherectomy (N = 512)	Angioplasty (N = 500)	P Value
	no. (%)		
Death	8 (1.6)	3 (0.6)	0.22
Myocardial infarction	39 (7.6)	22 (4.4)	0.04
Coronary-artery bypass surgery	42 (8.2)	34 (6.8)	0.39
Need for subsequent non-surgical coronary intervention	145 (28.3)	152 (30.4)	0.48
No adverse clinical end point	307 (60)	307 (61)	0.68

*For the cumulative end points, patients may be included in more than one category. In addition, the six-month composite clinical end point was prospectively defined as death, the worst outcome, followed in order of rank by myocardial infarction, coronary artery bypass surgery, and the need for subsequent coronary intervention. Patients were classified in the category that corresponded to the worst event they had experienced. By ordinal logistic regression, there was no significant difference between the two groups in the composite clinical end point (P = [illegible]).

Appendix

In addition to the study authors, the following investigators and study groups participated in the Coronary Angioplasty versus Excisional Atherectomy Trial. *Cleveland Clinic Foundation, Cleveland:* L. Franco, R. Raymond, and S. Deluca; *Loyola Medical Center, Chicago:* S. Johnson, E. Grassman, B. Lewis, and L. Wrona; *St. Vincent's Hospital, Indianapolis:* T. Peters and B. Ness; *Klinikum Grosshadern der Universität, Munich, Germany:* T. Kuhn; *Carolina's Medical Center, Charlotte, N.C.:* R.M. Bersin, J. Gelorkhalo, B. Wilson, and S. Langelbach; *Jewish Hospital, Louisville, Ky.:* V. Mirovic; *Midwest Heart Research Foundation, Lombard, Ill.:* L.S. McKeever, J. Marek, P. Kerwin, and E.L. Enger; *Graduate Hospital, Philadelphia:* K.S. Gottlieb and H. Hunter; *Maimonides Medical Center, Brooklyn, N.Y.:* J. Shani and N. Schulhoff; *University of Louvain Medical School, Brussels, Belgium:* W. Wijns, J. Renkin, and T. Baudhuin; *Methodist Hospital, Memphis, Tenn.:* F. Martin and K. Garrison; *[illegible], Rotterdam, the Netherlands:* P.J. de Feyter and V. [illegible]; *St. Vincent's Medical Center, Bridgeport, Conn.:* E. Kosinski and M. Cagasan; *Johns Hopkins Hospital, Baltimore:* J. Brinker, M. Mulen, J.R. Resar, and V.J. Gianolas; *St. Francis Hospital, Blue Island, Ill.:* M. Cohen, M. Hickman, and F. Cross; *St. Joseph's Hospital, Atlanta:* W. Knopf, G. Cates, and J. Shafer; *Washington Cardiology Center, Washington, D.C.:* K. Kent, A. Pichard, L. Satler, J. Popma, and P. Sherry; *Maine Medical Center, Portland:* M. Kellett, Jr., J. [illegible], and J. Kane; *Boston University Medical Center, Boston:* A. Jacobs, D.P.

Farou, and M. Marcu; *Minneapolis Heart Institute, Minneapolis:* M. Mooney, J. Madison, and R. Nowicki; *Mayo Foundation, Rochester, Minn.:* K. Garratt, J. Bresnahan, and J. Ramsdale; *Ochsner Foundation Hospital, New Orleans:* C.J. White, E. Ramee, and B. Lassara; *Riverside Methodist Hospitals, Columbus, Ohio:* A. Chapekis, N.H. Kander, B.S. George, N. Kander, and C. Gilliland; *Southwest Cardiology Presbyterian Hospital, Albuquerque, N.M.:* H.J. White and K. Sexton; *Georgetown University, Washington, D.C.:* S.N. Oesterle and L. Barry; *Rhode Island Hospital, Providence:* B. Sharaf and M. Gregory; *University of Louisville, Louisville, Ky.:* D.J. Talley and Z. Yassanan; *Sequoia Hospital, Redwood City, Calif.:* L. Baudrey; *Emory University Hospital, Atlanta:* S. Mezdi; *St. Vincent Hospital, Portland, Oreg.:* P. An, H. Gordon, and T. Gleckman; *University of Washington, Seattle:* D.K. Stewart, J. Chambers, and J. Dahlquist; *Beth Israel Hospital, Boston:* K. Kuntz, D. Baim, and C. Senerchia; *Christ Hospital, Cincinnati:* D. Kereiakes, C. Abbottsmith, and D. Lausten; *Good Samaritan, Phoenix, Ariz.:* M. Fashick, J. Schumacher, and A. Stephens; and *Medical College of Virginia, Richmond:* M. Cowley and K. Kelly.

Coordinating Center: R.M. Califf, L.G. Berdan, K.L. Lee, G. Kesler, T. Allen, M. Liu, K. Lucas, K. Pieper, J. Snapp, and P.L. Mends. *Angiography Core Laboratory:* S.G. Ellis, D. Debowey, T.D. Crowe, T.R. Ivanc, H.B. Vilsack, J.A. Merriam, D.J. Green, D.L. Fisher, and S. Brand. *Core Pathology:* J.M. Isner, M. Kearney, K. Wills, C. Loushin, and S. Bowman. *Data and Safety Monitoring Committee:* H.C. Smith, A. Guerci, N.S. Kleiman, K.L. Lee, D.B. Mark, J. Tcheng, and W.D. Weaver. *Economics and Quality of Life Coordinating Center:* D.B. Mark, L. Davidson-Ray, L.C. Lam, C. Moore, L. Larson, and L.M. Bayadro. *Operations Committee:* E.J. Topol (study chairman), S. King, M. Cowley, D.O. Williams, T. Hinohara, P. Serruys, K. Kent, and R.M. Califf. *Financial Center:* V. Stoski, D. Shrein, and D. Passmore.

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CORD078497

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Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months*

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Summary

Restenosis after coronary angioplasty occurs in at least 30% of patients in the first six months and, as yet, there is no known treatment to decrease this event. We tested a monoclonal antibody Fab fragment (c7E3) directed against the platelet glycoprotein IIb/IIIa integrin, the receptor mediating the final common pathway of platelet aggregation, to see whether it reduced the frequency of clinical restenosis.

Patients who had unstable angina, recent or evolving myocardial infarction, or high-risk angiographic morphology, were randomised to receive c7E3 bolus and a 12 hour infusion of c7E3 (708 patients), c7E3 bolus and placebo infusion (695 patients), or placebo bolus and placebo infusion (696 patients). With maintenance of the double-blind state, patients were followed-up for at least 6 months to determine the need for repeat angioplasty or surgical coronary revascularisation and the occurrence of ischaemic events.

By 30 days, 12·8% of placebo bolus/placebo infusion patients had had a major ischaemic event (death, myocardial infarcton, urgent revascularisation), compared with 8·3% of c7E3 bolus/c7E3 infusion patients, yielding a 4·5% difference (35% reduction, p = 0·008). At 6 months, the absolute difference in patients with a major ischaemic event or elective revascularisation was 8·1% between placebo bolus/placebo infusion and c7E3 bolus/c7E3 infusion patients (35·1% vs 27·0%; 23% reduction p = 0·001). The favourable long-term effect was mainly due to less need for bypass surgery or repeat angioplasty in patients with an initial successful procedure, since need for repeat target vessel revascularisation was 26% less for c7E3 bolus/c7E3 infusion than for placebo treatment (16·5% vs 22·3%; p = 0·007). The c7E3 bolus/placebo infusion group had an intermediate outcome which was not significantly better than that of the placebo bolus/placebo infusion group.

These results extend the benefit of c7E3 bolus/c7E3 infusion from reducing abrupt closure and acute-phase adverse outcomes to a diminished need for subsequent coronary revascularisation procedures. Because this therapy carries a risk of bleeding complications and has been studied only in high-risk angioplasty patients, further evaluation is needed before it can be applied to other patient groups.

Lancet 1994; **343**: 881–86

Introduction

Restenosis after balloon angioplasty and percutaneous coronary interventions is common, leading to recurrence of anginal symptoms and the need for repeat revascularisation procedures in more than 25% within 6 months, at a cost of more than $2 billion per year in the US.[1-4] The main cause of restenosis is vascular injury, induced by the inflated balloon or alternative device, accompanied by platelet-thrombus formation and change of phenotype of medial smooth muscle cells from their resting contractile state to one capable of migratory, proliferative, and secretory function.[5-7] Although various drugs have been successful in experimental models in altering the characteristic myointimal growth that occurs after vascular injury, no agent has proved effective in a large-scale clinical trial.[1,4,8,9]

Coronary angioplasty is routinely performed with adjunctive oral aspirin and intravenous heparin. However,

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this anti-thrombotic approach only weakly inhibits platelet aggregation. Various agonists, including thrombin, collagen, and ADP, can stimulate platelets even in the face of aspirin therapy.[10] The final common pathway for platelet aggregation involves glycoprotein IIb/IIIa integrin[10,11] to which a chimeric 7E3 antibody Fab (c7E3) fragment can selectively bind. The antibody consists of a humanised murine monoclonal IgG molecule. After pilot studies confirmed preliminary safety and efficacy of c7E3 Fab fragment,[12,13] we performed an acute phase multicentre, double-blind, placebo-controlled trial in 2099 patients.[14]

In addition to studying the acute phase effects we hypothesised that c7E3 would be capable of reducing clinical restenosis, as defined by ischaemic events or the need for repeat revascularisation, during the follow-up.

Patients and methods

2099 patients were included in the trial. Patients were eligible if they needed coronary angioplasty or directional atherectomy and had an evolving or recent myocardial infarction (MI), unstable angina, or high risk angiographic lesion morphology or clinical characteristics.[15] Patients were excluded if they had a tendency to bleed, were aged above 80 years, had had a stroke within the past 2 years, or had had major surgery up to 6 weeks before study entry. The protocol was approved by the institutional review board at all 56 participating sites and informed consent was obtained from all patients.

Patients received oral aspirin 325 mg per day, with the first dose given at least 2 hours before the procedure. Intravenous heparin was given during the procedure to ensure an activating clotting time of at least 300 seconds. Patients were then randomly assigned to one of three groups: placebo bolus and placebo 12 hour infusion; active c7E3 (Centocor, Malvern PA) bolus at 0·25 mg/kg and placebo 12 hour infusion; or active c7E3 bolus at the same dose followed immediately by c7E3 infusion at 10 μg/min for 12 hours. The bolus was given at least 10 minutes before the coronary procedure.

The primary endpoint was the 30-day composite incidence of death from any cause, MI, coronary artery bypass surgery, repeat percutaneous coronary angioplasty (PTCA), or need for an endoluminal stent or insertion of an intra-aortic balloon pump to treat ischaemia. All events were reviewed by an independent clinical endpoints committee, which remained blinded to treatment and required consensus of at least two reviewers for classification. During six month follow-up, the double-blind state was preserved. There has been no unblinding of the assignment data to any of the investigators, except in 36 patients who were undergoing emergency bypass surgery and 46 patients with bleeding complications in the acute phase.[14]

The primary endpoint for 6 month outcome was the composite of death, nonfatal MI, or the need for a repeat revascularisation (PTCA, coronary artery bypass surgery, or both). Stenting or the use of an intra-aortic balloon pump was not included as an outcome after 30 days, as it was in the acute-phase analysis, since the focus was the need for revascularisation rather than surrogates for a sudden ischaemic event. Diagnosis of myocardial infarction after hospital discharge required either a new significant Q-wave equal to or above 0·04 sec in duration or with a depth above one-quarter of the corresponding R wave amplitude in two or more contiguous leads; or a creatinine kinase or creatinine kinase myocardial band greater than twice the upper limit of normal. Revascularisation data were collected, including repeat surgical or percutaneous procedures on the original target vessel. Follow-up was 99% complete. All but 21 of the 2099 patients had their follow-up survival status determined; of the remaining patients, 17 refused to continue participation, 3 had relocated to other countries, and 1 was devastated by a hurricane.

Our analysis included all events from baseline to 6 months, events occurring after the 30-day endpoint in patients with an initial successful intervention (defined as achievement of a final stenosis less than 50% and without an ischaemic complication),

Patients with successful index PTCA evaluated after day 2	Placebo (n=600)	Bolus (n=606)	Bolus and infusion (n=820)
Risk factors			
Diabetes	155 (25·8%)	146 (24·1%)	139 (22·4%)
Hypertension	321 (53·5%)	329 (54·4%)	314 (50·6%)
Elevated cholesterol	316 (52·7%)	337 (55·7%)	324 (52·3%)
Smoking	377 (62·8%)	428 (70·7%)	423 (68·2%)
Vascular disease			
Peripheral	47 (7·8%)	52 (8·6%)	52 (8·4%)
Cerebral	21 (3·5%)	19 (3·1%)	27 (4·4%)
Previous MI			
>30 days	109 (18·2%)	126 (20·8%)	128 (20·6%)
8–30 days	45 (7·5%)	55 (9·1%)	57 (9·2%)
<8 days	171 (28·5%)	185 (30·6%)	182 (29·4%)
Prior PTCA	145 (24·2%)	121 (20·0%)	139 (22·4%)
Prior CABG	88 (14·7%)	85 (14·0%)	95 (15·3%)
Coronary anatomy			
One vessel disease	334 (55·7%)	322 (53·2%)	354 (57·6%)
Two vessel disease	170 (28·3%)	198 (32·7%)	191 (30·8%)
Three vessel disease	93 (15·5%)	83 (13·7%)	75 (12·1%)
Type of procedure			
Balloon	538 (89·7%)	544 (89·9%)	556 (89·7%)
Atherectomy	29 (4·8%)	25 (4·1%)	31 (5·0%)
Both	33 (5·5%)	36 (6·0%)	33 (5·3%)
Target vessel			
LAD	241 (40·2%)	229 (37·9%)	262 (42·3%)
LCX	144 (24·0%)	159 (26·3%)	165 (26·6%)
RCA	234 (39·0%)	253 (41·8%)	219 (35·3%)
Left main	4 (0·7%)	1 (0·2%)	3 (0·5%)
Graft	35 (5·8%)	35 (5·8%)	43 (6·9%)

Table 1: Demographic features of patients with a successful initial procedure

and events occurring after 48 hours in patients with an initial successful intervention. The 30-day endpoint was prospectively selected because of precedent in many cardiovascular intervention trials;[14] the 48-hour cutoff was used because almost all abrupt closure events that happen after coronary intervention take place within this time.[16-18]

Randomisation was done by a telephone call to the Duke coordinating centre and stratified by study site and whether the patient was having an acute myocardial infarction. Data were collected by study coordinators on a separate 6 month case-report-form that was quality assured by blinded study monitors before data entry. The sponsor (Centocor) remained blinded to the follow-up results until all patients had completed follow-up. The events were adjudicated by the endpoints committee.

Statistical analysis

Most comparisons were by intention-to-treat; cumulative event rates, estimated with Kaplan-Meier and survival curves[19] were used to display the results graphically. Comparisons between placebo and each of the c7E3 arms was done with scores 0, 1, and 2 respectively, by use of the log rank statistic. Proportional hazards (Cox) models were used to examine possible associations between baseline patient characteristics and outcome. These were done with all treatment groups to examine for differences between treatment arms. Proportional hazards regression (Cox) models were used after the 48-hour follow-up to examine factors which might be associated with late events or treatment effects. The factors included were treatment, revascularisation of single lesion or multiple lesions, duration of the procedure, and myocardial infarction or unstable angina at baseline against other high-risk entry criteria, such as gender, age greater than 65 years or less than 65 years, weight, and diabetes mellitus.

Results

The study enrolment began on Nov 26, 1991, and ended on Nov 18, 1992, with 2099 patients. The baseline characteristics of the patients who had a successful initial angioplasty or atherectomy procedure, without the need for a repeat urgent procedure in the first 48 hours, are presented in table 1. There were no significant differences

	Placebo	Bolus	Bolus + infusion	p-value pairwise
Events of all patients enrolled	(n=696)	(n=695)	(n=708)	
Death	3·4	2·6	3·1	0·832
MI	10·5	8·0	6·9	0·016
CABG	10·9	9·9	9·4	0·343
PTCA	20·9	19·9	14·4	0·001
Composite (death, MI, CABG, PTCA)	35·1	32·6	27·0	0·001
Any revascularisation (CABG/PTCA)	29·4	28·6	22·7	0·004
Target vessel repeat revascularisation	22·3	21·0	16·5	0·007
Events of all patients after 48 hours	(n=606)	(n=618)	(n=639)	
Death	2·7	2·3	3·0	0·660
MI	2·6	2·4	2·5	0·866
CABG	7·6	7·7	7·0	0·705
PTCA	18·5	17·1	11·6	0·011
Composite (death, MI, CABG, PTCA)	25·4	24·3	19·2	0·007
Any revascularisation (CABG/PTCA)	23·0	22·5	18·0	0·025
Target vessel repeat revascularisation*	19·0	18·6	15·7	0·135
All patients with no event at 30 days	(n=549)	(n=576)	(n=598)	
Death	1·7	1·3	1·5	0·795
MI	2·0	1·9	1·7	0·723
CABG	5·6	6·0	4·7	0·446
PTCA	12·6	14·3	10·1	0·182
Composite (death, MI, CABG, PTCA)	19·3	20·3	15·3	0·071
Any revascularisation (CABG/PTCA)	17·5	18·8	14·5	0·161
Target vessel repeat vascularisation*	16·9	16·8	14·4	0·285

CABG = coronary artery bypass graft; PTCA = percutaneous coronary intervention; MI = myocardial infarction.
Pairwise comparison of bolus and infusion compared with placebo.
*Analysis of patients with initial successful PTCA.
The after 48-hour and after 30 days analyses include only patients who did not experience an end point in the preceding time interval.

Table 2: **Outcome at six months (%)**

in baseline features of the patients who had a successful initial procedure by treatment assignment.

Patients receiving c7E3 bolus only, or c7E3 bolus/c7E3 infusion, had a significant increase in bleeding complications in the first 48 hours, with approximate doubling of packed red-blood-cell transfusion rate (placebo bolus/placebo infusion 7%, c7E3 bolus/placebo infusion 14%, c7E3 bolus/c7E3 infusion 17%, $p < 0.001$). With c7E3 there were no significant increases in thrombocytopenia and no allergic effects. The 12-hour infusion was not fully completed in 48 patients (7·0%) receiving placebo, 85 patients (12·5%) assigned to active bolus only, and 107 patients (15·8%) in the c7E3 bolus/c7E3 infusion group.

The outcomes of death, MI, and the need for coronary artery bypass surgery or repeat coronary intervention, with target vessel revascularisation, are shown for all patients

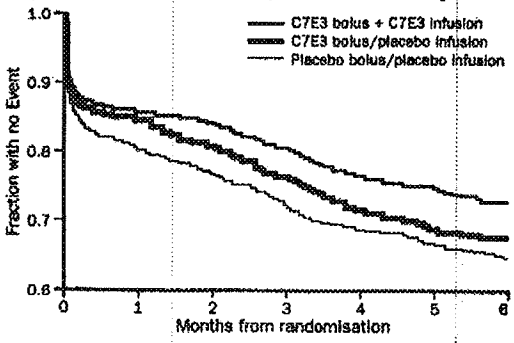

Figure 1: **Kaplan-Meier curve of all events (death, myocardial infarction, coronary revascularisation) for all patients enrolled**
There was a significant reduction of events for the c7E3 bolus/c7E3 infusion group compared with the active bolus only or placebo treatments ($p = 0.001$). A substantial proportion of events occurred after 1 month.

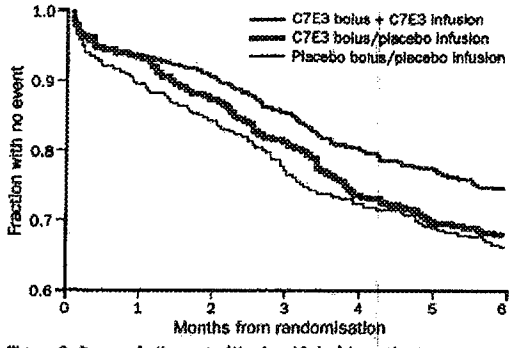

Figure 2: **Curve of all events (Kaplan-Meier) in patients with an initial successful coronary intervention**
Events were significantly reduced with the c7E3 bolus and infusion ($p = 0.007$) with only little effect of the bolus.

enrolled (table 2). Figure 1 shows data for all events (death, nonfatal infarction, or need for coronary revascularisation) for all patients who were entered into the trial. For the acute-phase endpoint, 81% of events had occurred by 48 hours. This was similar across treatment groups (82·0% placebo, 79·7% c7E3/bolus placebo infusion 81·4% c7E3 bolus/c7E3 infusion). By considering events after the first 48 hours the elective target vessel revascularisation over six months is identified. There was little difference for subacute ischaemic events or elective revascularisation between c7E3 bolus/placebo infusion and the c7E3 bolus/c7E3 infusion groups until after the 30-day endpoint (figure 2).

In addition to the composite of death, MI, and revascularisation, it is helpful to focus on target vessel revascularisation only. For the patient cohort with an initial successful coronary intervention during the six month follow-up, there was a significant 26% reduction for the c7E3 bolus/c7E3 infusion groups compared with the other treatment groups (figure 3). There was little effect of the active bolus alone on target vessel revascularisaton during follow-up.

In subgroup analyses patients who at baseline had acute coronary syndromes (unstable angina, recent, or acute myocardial infarction) were compared with the remaining patients who had stable angina but high-risk angiographic morphology (table 3). This revealed significant reductions in composite events for both subgroups, but the reduced need for repeat coronary interventions was only significant

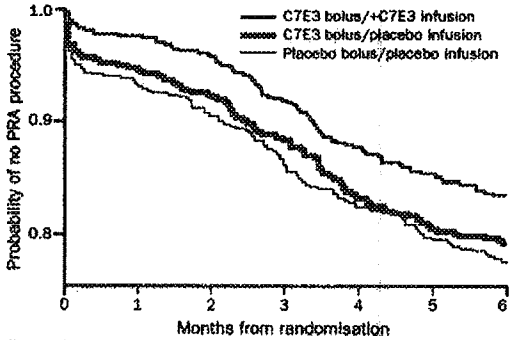

Figure 3: **Need for subsequent target vessel revascularisation, either by coronary angioplasty or coronary artery bypass surgery**
Repeat revascularisation was significantly reduced in the bolus and infusion group ($p = 0.007$).

	Placebo	Bolus	Bolus + infusion	p-value pairwise
Events until 6 months				
Acute coronary syndrome (n)	288	306	299	
Composite event	33·4%	29·0%	25·8%	0·037
Target vessel repeat revascularisation	20·2%	16·9%	15·4%	0·134
Stable angina (n)	408	389	409	
Composite event	36·2%	35·4%	28·0%	0·013
Target vessel repeat revascularisation	21·3%	22·1%	13·5%	0·003
Events from 48 h to 6 mo				
Acute coronary syndrome (n)	252	277	271	
Composite event	23·9%	21·5%	18·1%	0·089
Target vessel repeat revascularisation	14·6%	15·2%	11·9%	0·323
Stable angina (n)	354	341	368	
Composite event	26·5%	26·6%	19·9%	0·036
Target vessel repeat revascularisation	17·5%	18·7%	11·1%	0·010

PTCA: percutaneous coronary intervention.

Table 3: **Subgroup analysis of events for acute coronary syndrome versus stable angina patients**

in stable angina patients (table 3). This finding was consistent, whether events were analysed from baseline or after 48 hours in the patients with a successful procedure.

By regression analysis, the c7E3 bolus/c7E3 infusion treatment was independently associated with fewer events (death, MI, or need for revascularisation) during six month follow-up of an initially successful procedure (hazard ratio 0·75, $p = 0·025$). This was the only variable associated with fewer events; diabetes (hazard ratio 1·44, $p = 0·001$) and increased duration of the procedure (hazard ratio 1·09 for each 30 minutes of increased duration; $p = 0·012$) were the two variables associated with an increased event rate in follow-up. Symptom status at entry was not associated with either late events or treatment effects.

Discussion

Our findings show a reduced frequency of restenosis in patients who received c7E3 bolus/c7E3 infusion. The benefit at six months was a 23% reduction of ischaemic events (including death, nonfatal MI, and need for revascularisaton) and, among patients with an initially successful coronary intervention, a 26% decrease in target vessel revascularisation.

Our patients may not be fully representative of patients undergoing routine coronary intervention because of the requirement of a recent or ongoing acute coronary syndrome or high-risk coronary anatomy when entering the trial. The inclusion criteria emphasised possible intraluminal thrombus, which accompanies the clinical syndromes of unstable angina and acute MI, thereby increasing the likelihood that anti-thrombotic agents such as c7E3 might exert an effect. However, subsequent events were significantly diminished in patients without acute coronary syndromes. Regression analysis did not show differences in treatment effects for patients with recent acute coronary syndromes or stable angina. Whether this relates to the reduced power of subgroup analysis needs clarification. This point will require further study before the treatment can be extrapolated to routine patients undergoing coronary intervention.

The c7E3 Fab fragment has potent affinity for platelet IIb/IIIa surface integrin and binds with minimum dissociation. Our pilot studies in patients undergoing angioplasty showed that even when the infusion of antibody stops, there is persistent occupancy of the IIb/IIIa binding sites for at least 36 to 48 hours, and platelet aggregation is inhibited for at least 72 hours.[13,21] Although both effects diminish and revert to baseline over time, it is important to highlight the extended duration of c7E3 and the surprising finding that the active bolus by itself did not have a clinically meaningful effect on either acute or six month outcomes. This suggests that it is not possible to achieve the desired effects of reducing acute ischaemic events or clinical restenosis via brief IIb/IIIa inhibition, and raises the possibility that prolonged suppression of this integrin could be accompanied by further improvement of outcomes.

c7E3 is not solely selective for the glycoprotein IIb/IIIa receptor, but cross-reacts with the vitronectin receptor.[20] It is not clear whether this integrin has a role in modulating restenosis, but other IIb/IIIa receptor inhibitors have varying degrees of specificity with the target and homologous integrins.[21,22] Comparative clinical trials should clarify clinical relevance of the molecular differences.

We did not perform systematic six-month repeat angiography to determine quantitatively the extent of renarrowing in the treatment groups. This has been the standard approach in most restenosis trials,[5–7,23–25] but has a major drawback because diagnosis of target vessel stenoses in asymptomatic patients can lead to repeat procedures that would not have occurred in practice. Accordingly, our design offers a simulation of clinical practice in a large population of patients. The approach used in our trial would not be suitable for a chronically administered agent, especially if such an agent had an anti-anginal effect. Because the patients in our study were treated similarly except for the study drug bolus and infusion, and the double-blind state was carefully preserved until the follow-up was complete, it is difficult to invoke any other process besides a reduced arterial renarrowing to explain the clinical benefit. It is the net objective of restenosis trials to show reduced need for repeat revascularisation, because angiographic benefit, which has been documented in some recent restenosis trials, is not by itself adequate or completely clinically relevant. Furthermore, since death and MI are unusual in patients after PTCA, the main outcome that should be modulated is repeat target vessel revascularisation. Nevertheless, it would be helpful in subseqent studies to verify the effects of c7E3 and other IIb/IIIa inhibitors at the angiographic level.

Our study represents the first large-scale randomised trial to show a clinically meaningful reduction in the need for subseqent revascularisation procedures and therefore less clinical restenosis. We achieved this by blocking IIb/IIIa molecules with c7E3 antibody, thus reducing the reactivity of the arterial surface: from a surface that supports platelet deposition to one that does not.[26] Even though the infusion of c7E3 was only maintained for 12 hours, the agent has an extended anti-platelet effect lasting days and there was no evidence of rebound in ischaemic events in the acute phase. The independent benefit of reduced target vessel revascularisation at six months suggests a lasting effect of c7E3 and can be offered as clinical support for inducing passivity in the vessel wall, as has been suggested experimentally.[26–29]

The finding of less clinical restenosis with platelet IIb/IIIa blockade again emphasises the role of the platelet-thrombus, which has been put forward as a key element in the development of the post-angioplasty or endothelial injury neointimal lesion.[30–32] Although proliferation of medial smooth muscle cells may also play a part,[5–7] and the effect of c7E3 only partly limited clinical restenosis, our

findings suggest that potent anti-platelet and anti-thrombotic approaches to restenosis may be fruitful. The excess in bleeding events and transfusion requirement induced by c7E3[14] will need to be countered before such a prophylactic strategy can be widely adopted. Finally, the reduction of restenosis with platelet IIb/IIIa blockade is an extension of the previously demonstrated benefit of suppressing acute ischaemic events.[14] Our trial shows that the current approach of using aspirin during coronary intervention[33] as the sole anti-platelet strategy is insufficient to stop the platelet response to vascular injury.

Supported by a grant from Centocor, Inc.

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Double-blind randomised trial of very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer

Mark Levine, Jack Hirsh, Michael Gent, Andrew Arnold, David Warr, Anna Falanga, Martin Samosh, Vivien Bramwell, Kathleen I Pritchard, David Stewart, Pamela Goodwin

Summary

Patients receiving chemotherapy for metastatic breast cancer are at high risk of thromboembolic disease. Long-term oral anticoagulant therapy is needed but increases the risk of haemorrhagic complications. We have assessed the safety and efficacy of warfarin in very low doses as prophylaxis.

Women receiving chemotherapy for metastatic breast cancer were randomly assigned either very-low-dose warfarin (152 patients) or placebo (159). The warfarin dose was 1 mg daily for 6 weeks and was then adjusted to maintain the prothrombin time at an international normalised ratio (INR) of 1·3 to 1·9. Study treatment continued until 1 week after the end of chemotherapy. The average daily dose from initiation of titration was 2·6 (SD 1·2) mg for the warfarin group and the mean INR was 1·52. The mean time at risk of thrombosis was 199 (126) days for warfarin-treated patients and 188 (137) days for placebo recipients ($p = 0·45$). There were 7 thromboembolic events (6 deep-vein thrombosis, 1 pulmonary embolism) in the placebo group and 1 (pulmonary embolism) in the warfarin group, a relative risk reduction of about 85% ($p = 0·031$). Major bleeding occurred in 2 placebo recipients and 1 warfarin-treated patient. There was no detectable difference in survival between the treatment groups.

Very-low-dose warfarin is a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer who are receiving chemotherapy.

Lancet 1994; **343:** 886–89

See Commentary page 867

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Introduction

Thromboembolism has long been recognised as a complication of malignant disorders.[1] Mechanisms proposed for thrombosis associated with malignant disease include release of procoagulants by tumour cells and the simple explanation that such patients frequently have other predisposing factors, such as surgery, bed rest, and infection. Clinical trials in patients with breast cancer have shown the potential for anticancer drugs to induce both venous and arterial thrombosis.[2–5]

Subcutaneous heparin, pneumatic compression, and dextran are effective forms of prophylaxis in hospital in patients at high risk of venous thrombosis, such as surgical patients, but are not practicable for long-term use in patients receiving cancer chemotherapy as outpatients.[6] Oral anticoagulant treatment is effective as prophylaxis in surgical patients[6] and in patients with atrial fibrillation.[7,8]

Low-intensity warfarin therapy with an international normalised ratio (INR) of 2·0 to 3·0 is as effective as high-intensity warfarin (INR > 3·0) in the prevention of thromboembolism and is associated with less bleeding.[7] Such low-intensity warfarin regimens have been used in patients with established venous thrombosis, tissue or mechanical heart valves, and non-valvular atrial fibrillation.[8–11] However, even this low intensity of

EuroIntervention

EXHIBIT 8

One-year results of a durable polymer everolimus-eluting stent in *de novo* coronary narrowings (The SPIRIT FIRST Trial)

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This study was sponsored by Guidant Corporation, Santa Clara, California, USA.
Ms. Veldhof and Ms. Dorange are employees of Guidant Corporation. The other authors declare no conflict of interests.
Presented in part at The Scientific Sessions of The American Heart Association, Dallas, Texas, 13 - 16 November, 2005.

KEYWORDS
Coronary artery disease, eluting stent, everolimus, randomized trial

Abstract

Aim: Short-term results of durable polymer everolimus-eluting stents have shown significant improvements in clinical and angiographic outcomes. This report presents the 1-year clinical and angiographic data from the SPIRIT FIRST Trial.

Methods and results: This first-in-man single blind multi-centre randomized controlled trial assessed the safety and efficacy of everolimus and a durable polymer on a cobalt chromium stent in patients with *de novo* native coronary artery lesions. Of the 60 patients enrolled, a total of 56 patients (27 everolimus arm and 29 bare stent arm) were qualified to per-treatment analyses at 1 year. Quantitative angiographic and intravascular ultrasound (IVUS) analyses were performed. Angiographic late loss, IVUS neointimal volume obstruction and major adverse cardiac events (MACE) at 1 year were assessed as the study endpoints. At 1 year, the in-stent late loss and diameter stenosis of patients were 0.24 mm and 18% in the everolimus arm (n=20), as compared with 0.84 mm and 37% in the bare stent arm (n=25, $p < 0.001$). Significantly less neointimal hyperplasia was observed in the everolimus arm compared to the bare stent arm (neointimal volume, 13±9 mm^3 vs. 37±17 mm^3, $p < 0.001$; volume obstruction, 10±7% vs. 28±12%, $p < 0.001$). The overall MACE rate was 15.4% in the everolimus arm and 21.4% in the bare stent arm.

Conclusion: The safety and efficacy of everolimus-eluting stent with a durable polymer observed at 6 months was sustained at 1 year.

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Introduction

To date percutaneous coronary intervention (PCI) using drug-eluting stents is considered the most secure treatment option for *de novo* single coronary artery disease. The two clinically available stents coated with an anti-proliferative drug, sirolimus or paclitaxel, have shown promising clinical and angiographic outcomes as proven in several randomized trials[1-3]. Beside these two drugs, the efficacy of newly developed antiproliferative drugs has been clinically investigated[4-9] and their potent effects in preventing restenosis have been reported[5-9].

Everolimus is a powerful anti-proliferative agent and has shown effect in preventing rejection in kidney and heart transplantation[10-12]. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of DNA synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of FRAP (FKBP-12-rapamycin associated protein, also called mTOR, mammalian Target Of Rapamycin), this finding suggests that, like sirolimus, the everolimus-FKBP12 complex binds to and thus interferes with the function of FRAP.

The SPIRIT FIRST clinical trial represents the first evaluation of the everolimus-eluting stent which studied the potential benefits of the local application of everolimus in a durable polymer in combination with a stent with a thin strut design[5]. Compared to identical bare metal stents, everolimus-eluting stents have demonstrated effective suppression of neointimal growth at 6 months[5]. This paper presents the 1-year clinical and angiographic/intravascular ultrasound (IVUS) follow-up results from the experience with the durable polymer everolimus-eluting stent.

Methods

Study population

The SPIRIT FIRST clinical trial was a prospective, controlled, randomized, single-blinded, parallel 2-arm, multicentre clinical evaluation of a durable polymer everolimus-eluting stent (XIENCE™ V, Guidant, Santa Clara, CA, USA) in patients with *de novo* native coronary artery lesions. Patient eligibility criteria, device description and study procedure were previously reported, along with 6-month clinical, angiographic and IVUS analyses[5]. Briefly, study patients had single *de novo* stenoses of < 18 mm lesion length, coverable by 1 study stent, > 50% diameter stenosis, and vessel reference diameter 3.0 mm as assessed by on-line quantitative coronary angiography (QCA). Patients were ineligible if they had any of the followings: evolving myocardial infarction; stenosis of an unprotected left main coronary artery, an ostial location, or located within 2 mm of a bifurcation; a lesion with moderate to heavy calcification, or an angiographically visible thrombus; a left ventricular ejection fraction < 30%; were awaiting a heart transplant, or had a contraindication to aspirin, clopidogrel, heparin and any other drugs related to this study.

Follow-up and study endpoint

Clinical evaluation was scheduled at 1, 6, and 12 months with annual evaluation up to 5 years. Angiographic and IVUS imaging was obtained at baseline, 6- and 12-month follow-up.

The primary endpoint was in-stent late loss at 6 months. The major secondary endpoint was percent (%) in-stent volume obstruction at 6 months based on IVUS analysis. Other secondary endpoints included the followings: a) in-stent late loss at 1 year; b) in-segment late loss at 6 months and 1 year including proximal and distal evaluations; c) in-stent% volume obstruction at 1 year; d) in-stent and in-segment% diameter stenosis at 6 months and 1 year; e) in-stent and in-segment angiographic binary restenosis (ABR) at 6 months and 1 year; f) persisting incomplete apposition, late incomplete apposition, aneurysm formation, thrombus, persisting dissection at 6 months and 1 year; g) major adverse cardiac events (MACE) rate in-hospital and at 1, 6, 9 months and annually up to 5 years. MACE is comprised of death, myocardial infarction (MI), or clinically driven target lesion revascularization (TLR); g) acute device, procedural and clinical success. All deaths that could not be clearly attributed to another cause were considered a cardiac death. A non-Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase MB, in the absence of new Q waves on the surface electrocardiogram.

Quantitative Coronary Angiography evaluation

QCA was performed by means of the CAAS II analysis system (Pie Medical B.V., Maastricht, The Netherlands). In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference diameter, and% diameter stenosis. ABR was defined in every segment as diameter stenosis >50% at follow-up. Late loss was defined as the difference between MLD at post-procedure and MLD at follow-up.

Intravascular Ultrasound Analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased-array IVUS using automated pullback at 0.5 mm per second. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was also examined. A computer-based contour detection program (Curad B.V., Wijk bij Duurstede, The Netherlands) was used for automated 3-D reconstruction of the stented and the peri-stent segments. The lumen, stent boundaries and external elastic membrane were detected using a minimum cost algorithm. The stent volume (SV) and lumen volume (LV) were calculated according to Simpson's rule. The in-stent neointimal volume was calculated as "SV-LV". The % obstruction of the stent volume was calculated as in-stent neointimal volume/stent volume _100. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated *in vitro* and *in vivo*[13].

Statistical analysis

The primary endpoint and all trial endpoints were analyzed on the per-treatment evaluable population. Acute success was analyzed on the safety population. The per-treatment evaluable population consisted of patients who had no bailout and no major protocol deviations. The data for each patient were reviewed in a blinded

manner to determine whether the patient should be included in this analysis population. Analyses based on the per-treatment evaluable population were as "treated". Patients were included in the treatment arm corresponding to the study stent actually received.

The overall sample size calculation for this trial was determined based on the primary endpoint of in-stent late loss at 6 months and on the following assumptions: a single comparison of active to control; one-tailed t-test, unequal and unknown variances in the 2 groups being compared; $\alpha = 0.05$; true mean difference between the control group and the treatment group is 0.48 mm. This assumption was made based on the results of VISION Registry (mean late loss = 0.83 mm)[14], SIRIUS trial (mean late loss = 0.17 mm)[2] and TAXUS IV trial (mean late loss = 0.39 mm)[15]. Assuming the true mean late loss for the treatment group was 0.35 mm, the difference between the control group and treatment group is calculated as: 0.83 mm – 0.35 mm = 0.48 mm. The standard deviation was assumed to be 0.56 mm in the control group and 0.38 mm in the treatment group (based on the results of VISION Registry study and SIRIUS trial with standard deviation for DES adjusted downward from 0.44 mm to 0.38 mm to take into account of 6-month angiography as opposed to 8-month angiography); approximately 20% rate of lost to follow-up or dropout; approximately 10% of patients with bailout stents; given the above assumptions, enrolling 30 patients per arm (analysis of 22 evaluable patients per arm) would have provided 95% power for comparison. Although the trial was not powered based on the major secondary endpoint, percent volume obstruction at 180 days, enrolling 30 patients per arm (analysis of 22 patients per arm) provides more than 96% power. Binary variables were compared using Fisher's exact test. For continuous variables, means and standard deviations were calculated and groups compared using the Wilcoxon's rank sum test. Time-to-event variables were compared with Kaplan-Meier analysis and the log rank statistic.

Results

A total of 60 study patients were randomized and consecutively enrolled at 9 investigational sites between December 2003 and April 2004. The safety population is composed of these 60 patients. Of the 60 patients, 3 were excluded from the per-treatment population (1 from the everolimus arm and 2 from the bare stent arm) because of bailout stenting (2) and major protocol deviation (1 patient on a heart transplant waiting list from bare stent arm). Hence the per-treatment population includes 56 patients (27 everolimus arm and 29 control) as illustrated in the trial profile (Figure 1). The control arm and the everolimus arm shared similar demographic characteristics except for patients with hypertension which was significantly higher in the everolimus group than in control (Table 1). Procedural characteristics were explained previously[5].

One-year quantitative coronary angiographic analysis (Table 2)

Nine patients did not have qualifying follow-up angiogram up to 1 year for the following reasons: a) patients withdrew from the clinical trial after the 30-day follow-up visit (1 patient in the everolimus

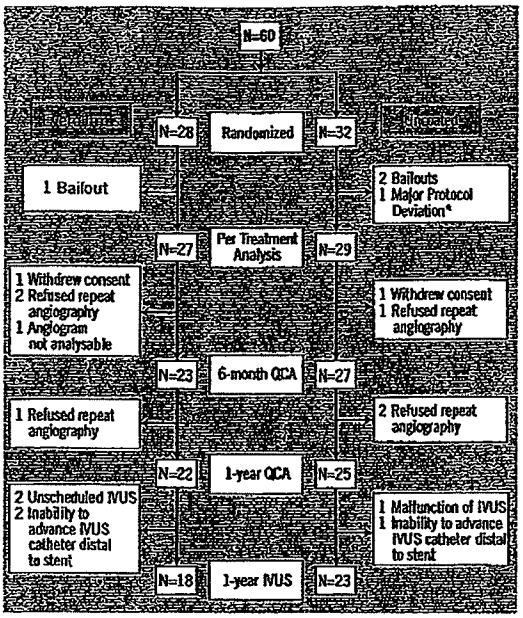

Figure 1. Flowchart of patients. QCA, quantitative coronary angiography; IVUS, intravascular ultrasound.

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment group.*

	Everolimus Stent (n=27)	Bare Metal Stent (n=29)	All Patients (n=56)
Age(yrs)	64±10	61±9	63±9
Male gender (%)	70	76	73
Current smokers (%)	28	31	30
Diabetes (%)	11	10	11
Hypertension requiring Medication (%)	70	41	55
Hyperlipidemia requiring Medication (%)	70	76	73
Prior intervention (%)	19	7	13
Prior MI (%)	24	14	19
Stable angina (%)	78	79	79
Unstable angina (%)	19	14	16
Target vessel (%)			
Left Anterior Descending	48	45	46
Left Circumflex	22	21	21
RCA	30	34	32
AHA / ACC# Lesion class (%)			
A	0	10	5
B1	41	28	34
B2	59	62	61
C	0	0	0
Reference vessel diameter (mm±SD)	2.61±0.40	2.71±0.28	2.66±0.34
Lesion length (mm±SD)	10.1±2.6	10.9±3.3	10.5±3.0

* There were no significant differences between the treatment groups except for Hypertension Requiring Medication (P=0.04)
# AHA / ACC = American Heart Association / American College of Cardiology

Table 2. Results of sub-segmental quantitative coronary angiographic analysis (Serial analysis)

	Proximal edge			In-Stent			Distal edge			In-segment analysis		
	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value	Everolimus-Stent (n = 20*)	Uncoated Stent (n = 25*)	P-value
Reference vessel diameter (mm)												
After procedure	2.81±0.36	2.98±0.33	0.27	2.74±0.29	2.80±0.32	0.61	2.70±0.31	2.71±0.32	0.95	2.69±0.33	2.74±0.34	0.81
At 6 months	2.79±0.34	2.64±0.43	0.10	2.74±0.31	2.57±0.39	0.12	2.66±0.37	2.44±0.38	0.06	2.65±0.36	2.58±0.38	0.50
At 1 year	2.75±0.34	2.64±0.39	0.29	2.65±0.32	2.52±0.38	0.22	2.59±0.39	2.40±0.39	0.12	2.59±0.37	2.53±0.38	0.62
Minimal luminal diameter (mm)												
After procedure	2.56±0.44	2.60±0.43	0.93	2.40±0.25	2.42±0.26	0.91	2.29±0.38	2.20±0.45	0.54	2.15±0.32	2.11±0.37	0.56
At 6 months	2.47±0.49	2.15±0.51	0.04	2.28±0.33	1.53±0.40	< 0.001	2.23±0.32	1.99±0.46	0.08	2.07±0.38	1.49±0.39	< 0.001
At 1 year	2.44±0.47	2.12±0.48	0.03	2.16±0.37	1.58±0.44	< 0.001	2.26±0.38	1.96±0.43	0.05	2.01±0.41	1.52±0.42	< 0.001
Late loss (mm)												
At 6 months	0.09±0.19	0.45±0.42	<0.01	0.12±0.22	0.89±0.39	< 0.001	0.06±0.21	0.21±0.41	0.10	0.08±0.20	0.62±0.39	< 0.001
At 1 year	0.12±0.25	0.48±0.39	< 0.001	0.24±0.27	0.84±0.45	< 0.001	0.03±0.25	0.25±0.42	0.04	0.14±0.24	0.59±0.42	< 0.001
Diameter stenosis (%DS)												
After procedure	9±11	13±9	0.53	12±6	13±7	0.36	15±10	19±11	0.22	20±6	23±9	0.18
At 6 months	12±14	18±18	0.17	17±7	41±14	< 0.001	16±8	19±14	0.95	22±11	42±13	< 0.001
At 1 year	11±13	19±15	0.12	18±13	37±17	< 0.001	13±8	18±14	0.24	22±15	40±16	< 0.001

*Patients who underwent angiography at 6 months as well as 1 year.

arm and 1 in the control arm); b) patients refused (3 in the everolimus arm and 3 in the control arm); c) angiogram was not analyzable (1 in the everolimus arm). Serial angiographic follow-up data, which is reported in this paper, were available in 80.4% (45/56) of the per-treatment population, with 74.1% (20/27) in the everolimus arm and 86.2% (25/29) in the control arm (Table 2). The follow-up in-stent MLD was significantly larger in the everolimus arm than in the control arm and the preservation of MLD between 6 months and 1 year was observed (2.28±0.33 mm at 6 months; 2.16±0.37 mm at 1 year) The mean in-stent late loss and% diameter stenosis were 0.24 mm and 18%, respectively, in the everolimus-stent group, as compared with 0.84 mm and 37%, respectively, in the control arm ($p < 0.001$ for each comparison). Figure 2 shows the cumulative frequency of in-stent late loss immediately after the index procedure at 6 months and 1 year in each treatment group. The late luminal loss at both the proximal and the distal edges of the stent was less in the everolimus-stent group than in the control arm ($p < 0.001$ for proximal and $p = 0.04$ for distal). The in-segment late loss was significantly less in the everolimus arm than in the bare stent arm ($p < 0.001$).

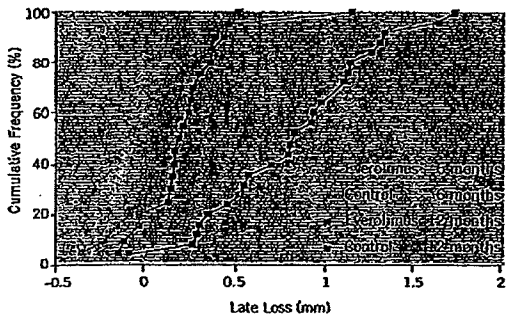

Figure 2. Cumulative frequency of late loss (in-stent) immediately after stenting.

One-year intravascular ultrasound evaluation (Table 3)

In this 1-year report, data in patients who underwent IVUS at 6 months as well as 1 year were presented to identify the volumetric change in serial IVUS examination. Forty-one patients (18 in the everolimus arm; 23 in the control arm) out of 47 patients with 1-year angiography underwent a 1-year IVUS examination. In the remaining

Table 3. Serial IVUS measurements at 1 year follow-up

		Everolimus-Stent (n = 18*)	Uncoated Stent (n = 23*)	P-value
Vessel volume (mm³)	6 months	296±90	291±74	0.89
	1 year	286±80	290±72	0.82
Stent volume (mm³)	6 months	137±31	138±31	0.94
	1 year	133±27	137±32	0.79
In-stent neo-intima volume (mm³)	6 months	9±12	39±20	< 0.001
	1 year	13±9	37±17	< 0.001
Luminal volume (mm³)	6 months	128±34	98±29	0.03
	1 year	120±30	100±28	0.15
In-stent volume obstruction (%)#	6 months	7±9	29±14	< 0.001
	1 year	10±7	28±12	< 0.001

* Patients who underwent IVUS at 6 months as well as 1 year.
# In-stent volume obstruction=100*(In-stent neo-intima volume/Stent volume)

6 patients, IVUS was not available: 2 were not properly scheduled for IVUS, 2 inability to advance IVUS catheter distal to stent in the everolimus arm; 1 malfunction of IVUS, 1 inability to advance the IVUS catheter distal to the stent in the control arm. Of the 41 patients, 37 patients (16 in the everolimus arm; 21 in the control arm) had serial IVUS data. Everolimus-eluting stent was associated with a significantly reduced degree of in-stent neointimal hyperplasia as well as in-stent% volume obstruction compared to the bare metal stent (13±9 mm³ vs. 37±17 mm³, $p < 0.001$; 10±7% vs. 28±12%, $p < 0.001$), reaching a 64% reduction of the in-stent volume obstruction (Table 3). There was no late acquired or persisting stent malapposion observed either at 6 months or at 1 year.

Major adverse events and clinical outcomes

Table 4 provides results of MACE and target vessel failure for the time points of 1 year. Since the six months follow-up the 1-year results for the everolimus arm included 1 non-Q wave MI due to a spasm during the follow-up IVUS procedure and 2 additional TLRs by PCI. One of these patients had a delayed ballout (TLR) using a non-study drug eluting stent 21 days after the baseline procedure due to a dissection. In the control arm, 1 additional TLR by PCI was observed, this being the patient's 3rd TLR since the index procedure. The hierarchical MACE rate at 1 year was 15.4% for the everolimus arm and 21.4% for the bare stent arm (p=0.59). The MACE rate for the everolimus group increased from 7.7% (2/26) at 6 months to 15.4% (4/26) at 1 year. Three of the 4 overall MACE events in the everolimus group were non-study-device related events. One Q-wave MI was in a non-target vessel, one TLR was due to dissection during the procedure, and one non-Q-wave MI occurred during follow-up IVUS procedure. Total non-hierarchical clinically-driven TLR rates at 1 year were 7.7% in the everolimus arm and 21.4% in the control arm. No adverse effects related to everolimus or the durable polymer were noted. Kaplan-Meier survival estimates were performed for overall MACE (Figure 3). There was no stent thrombosis observed in both arms out to the 1-year time period.

Table 4. Hierarchical Major Adverse Cardiac Events at 1 year in Per-Treatment Population

Event	Everolimus Stent		Uncoated Stent	
	n=26	%	n=26	%
Cardiac death	0	0	0	0
Myocardial infarction	2	7.6	0	0
Q-wave	1	3.8	0	0
Non-Q-wave	1	3.8	0	0
Reintervention				
Clinically driven TLR-CABG	0	0	1	3.6
Clinically driven TLR-PCI	2	7.7	5	17.9
Clinically driven TVR-CABG	0	0	0	0
Clinically driven TVR-PCI	0	0	0	0
Target vessel failure	4	15.4	6	21.4
Major adverse cardiac events	4	15.4	6	21.4

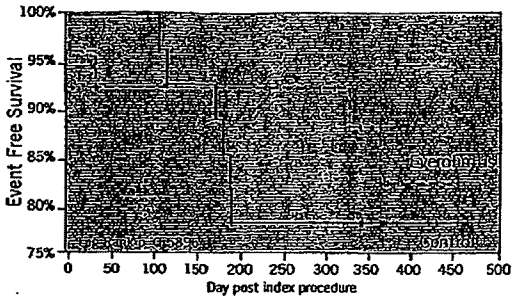

Figure 3. Kaplan-Meier survival curve: MACE. Since the 6-month time point, 1 non-Q wave MI due to a dissection during the follow-up IVUS procedure and 1 clinically-driven additional target lesion revascularization by PCI were observed in everolimus arm. In the control arm, 1 clinically-driven additional target lesion revascularization by PCI was performed.

Discussion

One-year clinical and angiographic follow-up from this trial demonstrates that the polymer-controlled release of everolimus from a coronary stent is safe and effective, with no late adverse effects. The superiority in efficacy, as measured by in-stent late loss, of everolimus-eluting stent as compared to bare stent was sustained at 1 year (71% reduction in late loss). The everolimus arm also maintained its superiority to the bare metal arm in the major secondary IVUS endpoint,% volume obstruction, at 1 year (64% reduction). In addition, the everolimus arm also continued to show significantly lower neointimal volume than the bare stent arm at 1 year (65% reduction).

The current strategy of local drug delivery using sirolimus and paclitaxel is the most promising approach to prevent restenosis, but, at the same time, the strategy has the potential liability for impairing endothelial recovery. Developing new compounds may improve on the potential side effects of the current drug-eluting stents, such as delayed healing with re-endothelialization[16] and fibrin[17], early[18] and late stent thrombosis[19]. In this trial, neither stent thrombosis nor other adverse effects related to the drug/durable polymer was observed out to the 1-year time point. On the other hand, an *in vitro* study has shown that sirolimus enhances tissue factor in human endothelial cell[20]. Effect of everolimus on endothelial cell and its similarity or difference compared to sirolimus will have to be investigated. The significant differences between sirolimus- and paclitaxel-eluting stents have recently been reported to likely exist with regard to angiographic as well as clinical outcomes[21,22]. "New comers" following these 2 pioneers could be competitors if they can, at least, demonstrate performance as effective as these 2 drug-eluting stents. Studies have suggested that angiographic assessment of late loss is associated with an increased restenosis rate[23,24] as well as a higher risk of TLR[25]. However, it still remains to be determined how to interpret the significance of the slight increase in late loss from 6 months (0.12 mm) to 1 year (0.24 mm) observed in this study stent. Moreover, delayed neointimal growth beyond the first 6 to 9 months has been reported in serial IVUS analyses in some trials

as documented in everolimus-eluting stent (in-stent volume obstruction, 7% at 6 months to 10% at 1 year), which may raise a concern about potential late catch-up phenomenon of DES[25]. Recent head-to-head comparative studies between sirolimus- and paclitaxel-eluting stent are still limited to short-term results[21,22,25,27-30]. Beneficial short-term outcomes do not necessarily translate in long-term efficacy. For example, late catch-up phenomenon has been experienced in vascular brachytherapy[31]. In this respect, the follow-up period of 1 year still seems relatively short to assess the durable safety and efficacy of one drug-eluting stent. However, neither sirolimus- nor paclitaxel-eluting stent have been associated with gradually increasing MACE over the years[32,33]. Therefore, we could expect a similar lasting treatment effect of this new eluting stent.

Study limitation

This study with a small patient population provided only safety and efficacy data. Two larger single-blind, randomized controlled studies (The SPIRIT II and SPIRIT III) further evaluating this study stent compared to the paclitaxel-eluting stent for the treatment of coronary artery disease are under way.

Conclusions

At 1 year, this trial demonstrated that the treatment effect observed at 6 months was sustained at 1 year for everolimus-eluting stent. The in-stent and in-segment late loss in the everolimus arm was reduced by 71% and 78% compared to those in the bare metal arm, respectively. These observations were consistent with IVUS measurements. The 1-year results showed a reduction of neointimal volume by 65% as compared to bare metal stent. A small increase in % volume obstruction in event-free patients was observed from 6 to 12 months, but is considered clinically insignificant. Both the angiographic and IVUS measurements showed that the patency of the target vessel treated with everolimus-eluting stent was maintained at 1 year.

Acknowledgement

The authors are grateful to the invaluable assistance of Stan Fink and Danny Detiège (Guidant, Santa Clara and Guidant Europe) for their valued assistance in reporting this study.

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1988 Vol 60 No 6

British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

British Medical Association

ASTM CODEN: BHJUAV 60(6) 459 542 (1988)
ISSN 0007-0769

Br Heart J 1988;60:485–8

Lack of effect of warfarin on the restenosis rate or on clinical outcome after balloon coronary angioplasty

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SUMMARY Between September 1985 and April 1987, 110 consecutive patients who had successful coronary angioplasty were included in a randomised prospective controlled evaluation of the effects of warfarin on restenosis. The warfarin (n = 56) and the control (n = 54) groups were not different in terms of age, sex, previous coronary bypass surgery or coronary balloon angioplasty, severity of symptoms, and frequency of multivessel disease or of total coronary occlusions. Warfarin was started on the day of the procedure and the dosage was adjusted to maintain the thromboplastin international normalised ratio ≥ 2·5. One hundred and five (96%) of the patients were given verapamil and other antianginal drugs were prescribed as needed. Low molecular weight dextran and heparin were given during the procedure and heparin was continued for 24 hours in all patients. One hundred and eight (98%) of patients were followed up clinically after a median of five months (range 1–20). Eighty five (77%) had follow up angiography at five months. In the warfarin group symptoms improved in 46 (85%) patients by at least 1 angina class and 31 (57%) were symptom free; the exercise test remained positive in 20 (36%) patients and the angiographic restenosis rate was 25% per lesion and 29% per patient. There were no major bleeding complications. In the control group 46 (85%) patients were improved by at least 1 angina class and 31 (57%) were symptom free; the exercise test was positive in 11 (21%) patients and the angiographic restenosis rate was 33% per lesion and 37% per patient. Although the incidence of angiographic restenosis tended to be lower with warfarin, none of these differences was significant.

These data suggest that the combination of verapamil and warfarin, in the absence of aspirin, is not significantly better than verapamil alone in preventing symptom recurrence or angiographic restenosis after coronary angioplasty.

Restenosis, usually occurring during the first three to six months after coronary balloon angioplasty, remains one of the main limitations of the technique.[1,2] Although several risk factors associated with an increased rate of recurrence have been identified,[1,3,4] our understanding of the underlying pathophysiological mechanisms remains incomplete, and no drug regimen has yet been shown consistently to affect the occurrence of restenosis.[5–7]

As it is currently understood, restenosis is a response to balloon induced arterial injury and is determined by multiple elements. Mechanical factors (elastic recoil of the dilated arterial segment, medial dissection, and intimal flap formation), haemostatic factors (thrombus formation and platelet deposition), and fibromuscular proliferation all occur and interact to induce restenosis.[8–10]

There is good experimental and clinical evidence that early local thrombus formation is a key element in restenosis.[11,12] Because of these data, and despite a previously reported negative result,[13] we undertook a prospective randomised controlled study of the effects of warfarin on the clinical outcome and angiographic restenosis rate after angioplasty.

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Accepted for publication 11 August 1988

Patients and methods

PATIENTS AND MEDICATION

Between September 1985 and April 1987, 155 consecutive patients underwent coronary artery balloon angioplasty at our hospital. The initial success rate was 76% for 140 stenoses and 47% for 15 occlusions—113 patients had a successful and

uncomplicated procedure (target lesion(s) with < 50% residual stenosis). One hundred and ten of these patients were randomly assigned to receive either warfarin and verapamil or verapamil alone after the procedure. Table 1 gives the baseline clinical data of both groups. Only lesions causing ≥ 70% stenosis were considered for angioplasty. All types of angioplasty were included—that is stenosis or occlusion, single or multivessel procedures, native vessels or vein grafts, primary stenosis or restenotic lesions (table 2). Twelve patients were included twice and two patients were included three times. During the study period, three patients were excluded before randomisation (one with a recent cerebrovascular accident that contraindicated the use of anticoagulants, one taking long term warfarin because of atrial fibrillation, and one who was successfully treated with streptokinase for recurrent chest pain with ST segment elevation a few hours after angioplasty).

All patients were given heparin 10 000 IU intravenously before angioplasty together with an infusion of low molecular weight dextran. Heparin was continued for 24 hours after the procedure, until the arterial sheath was taken out. Verapamil was started on the day of the procedure. In the anticoagulated group warfarin was begun on the evening of the angioplasty day. Dosage was adjusted to obtain a thromboplastin international normalised ratio of ≥ 2·5.[14] Verapamil and warfarin were continued either for six months or until a follow up angiogram was obtained. No antiplatelet agents were prescribed at discharge, but one patient in the warfarin group and six patients in the control group were given aspirin at some time during the follow up period. Aditional antianginal treatment such as nitrates or β blockers were given as required. There was no difference in the postoperative management of patients undergoing angioplasty of single or multiple lesions.

Table 1 *Clinical and angiographic data for warfarin and control groups*

Data	*Warfarin (n = 56)*	*Control (n = 54)*
Number	56	54
Mean age (SD)	56 (9)	57 (10)
Sex (% male)	88	83
CCS class 3 or 4	37 (66)	42 (77)
Unstable angina	6 (11)	13 (24)
Previous AMI	22 (39)	18 (33)
Previous CABG	7 (13)	11 (20)
Previous PTCA	13 (23)	9 (17)
Positive stress test	39/44 (89)	32/39 (82)
Multivessel disease	26 (46)	27 (50)

Except where indicated numbers in parentheses are percentages.
CCS, Canadian Cardiovascular Society; unstable angina, rest pain together with transient electrocardiographic changes; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

Table 2 *Angioplasty data for warfarin and control groups*

	Warfarin (n = 56)	*Control (n = 54)*
Lesion/patient (successfully treated)	1·2	1·3
Multilesion procedure	10 (18)	10 (19)
Multivessel procedure	3 (5)	4 (7)
Total occlusion*	4 (7)	2 (4)
Restenosis*	6 (11)	9 (17)
Target:		
LMS	0	1 (2)
LAD	33 (57)	32 (57)
LCX	7 (12)	6 (11)
RCA	13 (22)	14 (25)
VG	5 (9)	3 (5)

*Present in at least one of the target lesions for a given procedure.
Numbers in parentheses are percentages.
LMS, left main stem coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; VG, vein graft.

FOLLOW UP

Most patients were followed up as outpatients at the National Heart Hospital. For those who were unable to return, information was obtained from the referring physician whenever possible. Anticoagulation was monitored in anticoagulant clinics with regular checks of the international normalised ratio. Clinical follow up data, stress testing, and follow up angiograms were generally obtained three to nine months after angioplasty, or earlier if symptoms recurred or became worse.

END POINTS OF STUDY

Clinical state, the response of the ST segment to exercise, and the angiographic appearance of the angioplasty site were analysed at follow up. Before angioplasty and at follow up we used the Canadian Cardiovascular Society (CCS) grading system for subjective assessment of anginal symptoms. Unstable angina was defined as rest pain together with reversible electrocardiographic changes. The exercise test was symptom limited and done according to the modified treadmill Bruce protocol with monitoring of 12 electrocardiogram leads. ST segment depression of ≥ 1 mm developing in at least one lead during or after exercise was regarded as a positive test. Angiographic restenosis was considered to be present when there was ≥ 50% reduction in luminal diameter estimated from at least two projections at the site of the previous angioplasty.

We compared the results in the warfarin and the control groups by Student's *t* test for continuous variables and by the χ^2 test for discrete variables. Differences of $p < 0.05$ were considered to be statistically significant.

We calculated that for a power of 0·75 and a significance level of 0·05, we would need 54 patients in each group to show a 50% reduction in the restenosis rate.

Results

The two groups (warfarin and control) were similar for all the clinical and procedural variables tested (tables 1 and 2).

CLINICAL OUTCOME

At follow up we had subjective information on anginal symptoms for 108 (98%) of 110 patients (96% of the warfarin group and 100% of the control group). In the warfarin group (median follow up six months, range 1–18 months), 46 (85%) of 54 patients had improved by ⩾ 1 Canadian Cardiovascular Society angina class, and 31 (57%) were symptom free. Two patients (4%) were in class 4 and no patient had unstable angina. There were no major bleeding complications in the warfarin group. The results were similar for the control group (median follow up five months, range 1–20 months) where 46 (85%) of 54 were improved and 31 (57%) were symptom free. One patient (2%) was in class 4 and two had unstable angina (4%).

STRESS TESTING

Results of stress testing at follow up were available for 81 (74%) of 110 patients (75% of the warfarin group and 72% of the control group). In the warfarin group, 15 (36%) of 42 patients had an appreciable depression of the ST segment with exercise, and in 16 (38%) of 42 chest pain developed. The test was symptom limited and patients reached a median of Bruce protocol stage 3 (range 1–5). In the control group, eight (21%) of 39 patients had significant ST segment depression with exercise and in 12 (31%) chest pain developed. They reached a median of stage 3 of the Bruce protocol (range 0–5). None of these differences was statistically significant.

ANGIOGRAPHY

Angiographic follow up was obtained in 85 (77%) of 110 patients (75% of the warfarin group and 80% of the control group). After a median follow up of five months (range 1–19 months) in the warfarin group the restenosis rate was 29% per patient (12 of 42) and 25% per lesion (12 of 49). In the control group, the median follow up was five months (range 1–20 months), the restenosis rate per patient was 37% (16 of 43), and per lesion 33% (18 of 54).

During the follow up period in the warfarin group eight (15%) patients underwent a repeat angioplasty and two (4%) had elective coronary artery bypass grafting. Corresponding figures in the control group were nine (17%) and one (2%) respectively. There were no deaths in either group during the follow up period.

Discussion

Despite our initial hypothesis that warfarin would favourably affect clinical and angiographic outcome after coronary balloon angioplasty, we found that our results confirmed a previous finding[11] and did not show that oral anticoagulation had a significant effect on medium term results. This is the first comparison of the effects of anticoagulation with a control group that essentially had no antiplatelet treatment. Angiography showed that there was a trend towards a reduction in the restenosis rate for the patients in the warfarin group, and it could be argued that a larger study population might have shown a significant difference or have retrospectively identifed a subset in whom warfarin reduced the incidence of restenosis. However, in the absence of any difference in the subjective evaluation of anginal symptoms or electrocardiographic changes during stress testing, such an angiographic trend is difficult to interpret. The angiograms were analysed according to current clinical practice and the percentage reduction in the diameter at the angioplasty site was estimated visually. The angiographic views were standarised as far as possible and the films interpreted without knowledge of the individual's clinical condition. The cut off value of 50% taken to represent significant restenosis is widely accepted[10] but arbitrary. Our study was limited by the lack of quantitative computer assisted analysis of the angioplasty site.[15]

Compliance with the anticoagulation regimen after angioplasty has been reported to be less than ideal.[11] Because the patients in this series were regularly followed in anticoagulant clinics, compliance with treatment was good.

The timing of anticoagulation treatment in relation to angioplasty is probably an important factor, and in the present series there was a gap of 24–48 hours between the end of heparin administration after angioplasty and the establishment of effective oral anticoagulation. In view of the currently available data[11,12] such an interruption is probably undesirable, since the thrombosis and platelet deposition that contribute to restenosis may well occur at a very early stage. At the time when the study was designed it was thought that withdrawing the arterial sheath under full anticoagulation would cause problems, but experience with patients undergoing intracoronary stenting[16] has shown that it is feasible with few complications.

The best drug regimen for preventing restenosis

after angioplasty remains to be determined. Thornton *et al* reported that warfarin was no better than aspirin, and showed that aspirin was better than warfarin for patients with a long history of angina.[13] Fleck *et al* showed that interruption of aspirin treatment during follow up was associated with an increased risk of restenosis,[17] but their conclusions have been challenged by others.[16] Calcium channel blockers are widely prescribed after angioplasty, but currently there are no data to support this practice.[5 6]

Aspirin together with dipyridamole has recently been shown to reduce occurrence of acute closure after angioplasty,[18] and a similar combination is also known to be effective in maintaining patency in saphenous vein grafts.[19] Antiplatelet agents are currently being evaluated for their ability to prevent restenosis in several continuing controlled clinical trials.[7]

The effect of individual compounds on restenosis should be tested first. But the success of combination treatments with oral anticoagulants and one or several antiplatelet agents together may prove to be more important if the current interest in intravascular stenting devices[16] is maintained. This is because the initial thrombogenic properties of the currently used metallic stents means that empirical vigorous anticoagulation together with antiplatelet medication has been used during the first months after implantation.[16 20] If the restenosis rate is lower that that expected with conventional balloon angioplasty, the benefits derived from the mechanical support and those obtained by the drug regimen alone will have to be determined.

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